BACKGROUND DOCUMENT TO SUPPORT THE CFSAN FOOD ADVISORY COMMITTEE MEETING, DECEMBER 7-8, 2015

ADDRESSING *LISTERIA MONOCYTOGENES* IN READY-TO-EAT (RTE) FOODS

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I. Purpose

Protecting public health by ensuring a safe food supply is a critical responsibility of the U.S. Food and Drug Administration (FDA). Some subpopulations within the general population (such as pregnant women and their fetuses, the elderly, and those with underlying medical conditions (e.g. immunocompromised)) may be more susceptible to certain foodborne illnesses compared to the average healthy adult. FDA's policies need to protect these vulnerable subpopulations in addition to the general population.

In recent years, there have been several outbreaks of severe illness (invasive listeriosis) from the consumption of ready-to-eat (RTE) foods contaminated with the pathogen *Listeria monocytogenes*. These outbreaks have resulted in numerous cases of severe illnesses, including fatal cases. Although listeriosis occurs infrequently compared to other foodborne illnesses (e.g., 0.23 – 0.26 cases per 100,000 population for listeriosis versus 14.53 - 17.55 cases per 100,000 population for salmonellosis) (Johnson 2014), it has a relatively high mortality rate compared to most other foodborne pathogens (~20% compared to <1 % for *Salmonella* or *E. coli* O157) (Crerar 1996; de Valk 2005; Scallan 2011) and disproportionately affects the most vulnerable subpopulations. Several recent *Listeria* outbreaks associated with fresh or minimally processed fruits and foods such as ice cream have amplified the need to ensure that FDA's policies regarding *L. monocytogenes* are adequate to protect the health of the most vulnerable subpopulations when RTE foods are contaminated with *L. monocytogenes* (CDC 2011; CDC 2014a; CDC 2015a).

The purpose of this document is to (1) provide background on the regulatory framework for RTE foods; (2) provide background on *L. monocytogenes*; (3) present a chronological history highlighting past FDA policies intended to reduce the incidence of foodborne listeriosis; and (4) provide the most recent scientific information relevant to consider whether policies are adequate to protect the most vulnerable subpopulations and to encourage the development of *Listeria* control programs that are sufficiently robust to reduce the number of food products that become contaminated with *L. monocytogenes*.

II. Background on Regulatory Framework for Ready-to-Eat Foods

With few exceptions, our regulation entitled "Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food" (the CGMP and preventive controls rule; 21 CFR part 117) applies to any establishment that manufactures, processes, packs, or holds human food. One exemption is for farms, which are not subject to the CGMP and preventive controls rule. In general, farms that produce RTE fresh produce will be subject to the "Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption" (the produce safety rule; 21 CFR part 112).

With some exceptions, a food establishment that is required to register as a "food facility" is subject to requirements for hazard analysis and risk-based preventive controls in part 117. Exceptions are governed by specific exemptions established in the CGMP and preventive controls rule, such as for those food facilities that are very small businesses or are subject to our hazard analysis and critical control point (HACCP) regulations for juice (21 CFR part 120) or seafood (21 CFR part 123). A registered "food facility" must evaluate whether *L. monocytogenes* is a hazard requiring preventive controls and associated verification (such as sanitation controls verified through an environmental monitoring program) for any RTE food that is exposed to the environment prior to packaging when the packaged food does not receive a treatment or otherwise include a control measure (such as a formulation lethal to *L. monocytogenes*) that would significantly minimize *L. monocytogenes.*

III. Background on Ready-to-Eat Foods

We recently established a regulatory definition (21 CFR 117.3) for "RTE food" in the context of the CGMP and preventive controls rule. Under 21 CFR 117.3, an RTE food means any food that is normally eaten in its raw state or any other food, including a processed food, for which it is reasonably foreseeable that the food will be eaten without further processing that would significantly minimize biological hazards. We expect the regulated industry to have questions about how this definition applies to foods that bear cooking instructions. Consumer research indicates that consumer cooking practices are not uniform and that many consumers do not follow some cooking instructions, such as those on frozen foods or directions specifying that a product should be cooked until it reaches a certain temperature (Byrd-Bredbenner 2013; Lando 2010). In 2009, a prepackaged, refrigerated cookie dough was implicated in an *E. coli* O157:H7 outbreak that caused 76 confirmed cases of illness, including 35 hospitalizations (FDA/HHS 2009a; FDA/HHS 2009b). Although the pathogen was *E. coli* rather than *L. monocytogenes*, the outbreak demonstrates the potential for foods that bear cooking instructions to nonetheless be consumed without cooking and cause illness.

IV. Background on *Listeria monocytogenes*

Listeria monocytogenes is a Gram-positive bacterial pathogen that can cause foodborne illness ranging from mild illness (listerial gastroenteritis) to severe and often fatal illness (invasive listeriosis) (Painter and Slutsker 2007). Because *L. monocytogenes* is widespread in the environment, a food can become contaminated if ingredients in the food are contaminated with *L. monocytogenes* and have not been treated to destroy viable cells of this pathogen. Poor sanitary conditions or manufacturing practices may also lead to *L. monocytogenes* contamination of a food. For many foods, contamination with *L. monocytogenes* can be avoided by controls on ingredients, use of listericidal processes, segregation of foods that have been cooked from those that have not, and adherence to good manufacturing practices, especially proper cleaning and sanitation. Although *L. monocytogenes* generally is more heat resistant than other pathogens such

as *Salmonella* and *E. coli* O157:H7, it can be easily controlled in foods by thermal treatments (e.g., pasteurization) commonly used by the food industry.

L. monocytogenes is unusual in that it can remain viable after episodes of freezing and can grow at refrigeration temperatures, making it potentially problematic for both manufacturers and consumers who rely on refrigeration to inhibit bacterial growth (Hill 1995; Doumith 2004). Due to this potential for *L. monocytogenes* to grow during refrigerated storage, RTE foods have been subcategorized into foods that support its growth and foods that do not support its growth (Petran and Zottola 1989; Sorrells et al. 1989; Tienungoon et al. 2000; Russell and Gould 2003). In general, characteristics of an RTE food that does not support the growth of *L. monocytogenes* are as follows:

(1) The food has a pH less than or equal to 4.4; or

(2) The food has a water activity less than or equal to 0.92; or

(3) The food is customarily held and consumed in a frozen state; or

(4) The food is formulated to contain an effective listeristatic control measure (e.g. an antimicrobial substance or a combination of factors such as pH, water activity, and antimicrobial substances) (ICMSF 1996; Miller 1992)

In general, we consider that an RTE food supports the growth of *L. monocytogenes* if the food does not have the characteristics of RTE food that does not support growth.

Examples of RTE foods that support the growth of *L. monocytogenes* include:

- Milk;
- High fat and other dairy products (e.g., butter and cream);
- Soft unripened cheeses (greater than 50 percent moisture) (e.g., cottage cheese and ricotta cheese);
- Cooked crustaceans (e.g., shrimp and crab);
- Smoked seafood (e.g., smoked finfish and mollusks);
- Raw seafood that will be consumed as sushi or sashimi;
- Some deli-type salads and sandwiches (particularly those containing seafood and those prepared at retail establishments without acidification and/or the addition of antimicrobial substances)

Examples of RTE foods that generally are considered to not support the growth of *L. monocytogenes* include:

- Fish that is preserved by techniques such as drying, pickling, and marinating;
- Ice cream and other frozen dairy products;
- Process cheese (e.g., cheese foods, spreads, slices);
- Cultured milk products (e.g., yogurt, sour cream, buttermilk);
- Hard cheeses (less than 39 percent moisture) (e.g., Cheddar, Colby, and Parmesan);
- Some deli-type salads, particularly those processed to a pH less than 4.4 and those containing antimicrobial substances such as sorbic acid (or sorbates) or benzoic acid (or benzoates) under conditions of use documented to be effective in preventing the growth of *L. monocytogenes*;
- Crackers, dry breakfast cereals, and other dry foods.

The presence of *L. monocytogenes* in RTE foods presents a significant public health problem, especially if the food matrix supports its growth. However, illnesses can and do result from consumption of foods that do not support its growth (FDA-FSIS 2003; FAO/WHO 2004; FDA/HHS 2015a). Foods that have been implicated in outbreaks of invasive listeriosis include dairy products such as milk, whipping cream, butter, fresh soft cheeses (such as Queso Fresco), soft unripened cheeses (such as Ricotta), soft ripened cheeses (such as Brie), and ice cream. Other RTE foods implicated in outbreaks of invasive listeriosis include cantaloupes, sprouts, smoked mussels, smoked fish, and multi-ingredient prepared foods such as sushi, chicken salad (contaminated ingredient was fresh-cut diced celery), tuna salad, taco salad, potato salad, coleslaw (contaminated ingredient was cabbage), and caramel apples.

V. Highlights of the Science Regarding *Listeria* in Ready-to-Eat Foods as of 2008

A. 1996 Listeria *Publication*

A 1996 paper authored by FDA staff and entitled "U.S. position on *Listeria monocytogenes* in foods" (the 1996 *Listeria* publication) (Shank 1996) stated that, based on the available scientific information, FDA considered detection of *L. monocytogenes* in cooked, RTE foods to be a violation of section 402(a)(1) of the FD&C Act, in that the food bears or contains an added poisonous or deleterious substance which may render it injurious to health. The authors stated that FDA had established a "zero tolerance" for *L. monocytogenes* in cooked, RTE foods. The authors used the term "zero tolerance" to indicate that FDA considered any detectable level of *L.*

monocytogenes in cooked, ready-to-eat foods to be unacceptable from a public health perspective. The analytical method that FDA uses can detect 1 cfu of *L. monocytogenes* per 25 g of food to determine whether *L. monocytogenes* is present in the food (i.e., 0.04 cfu/g).

B. 2003 FDA/FSIS Listeria *Risk Assessment*

In 2001, FDA and the Food Safety and Inspection Service (FSIS) in the U.S. Department of Agriculture (USDA), in consultation with the Centers for Disease Control and Prevention (CDC) of the U. S. Department of Health and Human Services, requested comment on a draft quantitative assessment (the 2001 Draft *Listeria* risk assessment) (FDA/HHS 2001) of relative risk associated with consumption of 20 categories of RTE foods that had a history of contamination with *L. monocytogenes*, or that were implicated epidemiologically with an outbreak or a sporadic case of listeriosis. In 2003, FDA and USDA released their final risk assessment (2003 FDA/FSIS *Listeria* risk assessment) (FDA-FSIS 2003), which includes revisions made after review of comments received to the 2001 Draft *Listeria* risk assessment, including increasing the number of food categories to 23.

The purpose of the 2003 FDA/FSIS *Listeria* risk assessment was to examine systematically the available scientific data and information to estimate the relative risks of serious illness and death associated with consumption of different types of RTE foods that may be contaminated with *L. monocytogenes*. The 2003 FDA/FSIS *Listeria* risk assessment reports its results as a series of ranked relative risks based on both the estimated number of listeriosis cases that would result per serving (the "per serving relative risk") and the estimated annual number of cases (the "per annum relative risk"). Risk managers use the per serving relative risk to evaluate the probability that an individual would become ill from consumption of a particular food product, and use the per annum relative risk to evaluate which food categories have the highest potential to impact public health (i.e., the health of the U.S. population rather than the health of an individual).

For example, in 2003 deli meats had the highest per-serving risk (7.7×10^{-8}) as well as the greatest number of estimated fatal infections (1600), while pasteurized fluid milk had the 9th highest per-serving risk (1.0×10^{-9}) but second highest number of estimated fatal infections (90.8). Milk illustrates the concept that although a product may have a lower relative risk per serving, it could nonetheless have a higher number of expected cases of illness, owing to its relatively high consumption. Overall, the 2003 FDA/FSIS *Listeria* risk assessment concludes that RTE foods that support the growth of *L. monocytogenes* are much more likely than other foods to be associated with listeriosis.

The 2003 FDA/FSIS *Listeria* risk assessment estimates that only a small percent of contaminated servings would be highly contaminated (see Table III-17 in Section III, p. 75; FDA-FSIS 2003)(Miller 1992; ICMSF 1996). In addition, the 2003 FDA/FSIS *Listeria* risk assessment estimates that RTE foods that do not support growth of *L. monocytogenes* present a low or very low risk (as those terms are defined in the risk assessment) of listeriosis: less than 1 case per

billion servings and less than one case per year (see Table V-6 in Section V, p. 133; FDA-FSIS 2003). The 2003 FDA/FSIS *Listeria* risk assessment provides information grouping its results as a two-dimensional matrix with five overall risk designations (i.e. Very High, High, Moderate, Low, and Very Low). Although the 2003 FDA/FSIS *Listeria* risk assessment concludes that U.S. consumers are exposed to low to moderate levels of *L. monocytogenes* on a regular basis, it also concludes that susceptible populations are at a higher risk for *Listeria*-related disease than the general population. The 2003 FDA/FSIS *Listeria* risk assessment suggests that targeted strategies could decrease the number of *Listeria* infections (FDA-FSIS 2003).

In response to the findings of the 2003 FDA/FSIS *Listeria* risk assessment, FSIS conducted a complementary risk assessment to evaluate which food safety interventions during the processing of RTE meat and poultry products are most effective in preventing listeriosis (FSIS 2003a). This FSIS risk assessment revealed that formulating RTE products with growth inhibitors and using post lethality interventions, combined, were more effective in preventing foodborne illness, compared with using either of these interventions alone or with testing and sanitizing food-contact surfaces. These findings directly formed the scientific basis of FSIS's interim final rule for *L. monocytogenes*, which encourages federal establishments to adopt more effective food safety interventions during the production of RTE meat and poultry products (9 CFR 430; FSIS 2003b). FSIS also used these findings and those from the 2003 FDA/FSIS *Listeria* risk assessment to guide its verification sampling programs, whereby RTE meat and poultry processing establishments (9 CFR 430) with less effective *L. monocytogenes* controls are sampled more frequently (FSIS 2010). These findings were used to inform FSIS' compliance guidance to industry (FSIS 2014). To aid in implementation of the interim final rule, FSIS provided specialized training to its inspection workforce. These policies and programs have resulted in industry adoption of more stringent *L. monocytogenes* controls during the processing of RTE meat and poultry products in the U.S. Correspondingly, FSIS has observed a steady and substantive decline in the number of *L. monocytogenes*-positive samples from its in-plant testing programs, an indication that interventions during processing to mitigate risks from RTE meat and poultry products are succeeding (See Figure 1, p. 7; FDA-FSIS 2013).

C. 2004 FAO/WHO Listeria *Risk Assessment*

In 2004, the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) conducted a microbiological risk assessment of *L. monocytogenes* in RTE foods (2004 FAO/WHO *Listeria* risk assessment). The 2004 FAO/WHO *Listeria* risk assessment, prepared at the request of the Codex Committee on Food Hygiene (CCFH), was intended to provide a scientific basis for the development of guidelines for the control of *L. monocytogenes* in foods by member countries and focused on three specific estimations: (1) risk of serious illness from *L. monocytogenes* in food when the number of organisms ranges from absence in 25 grams to 1000 colony forming units (CFU) per gram or milliliter, or does not exceed specified levels at the point of consumption; (2) risk of serious illness for consumers in

different susceptible population groups (elderly, infants, pregnant women and their fetuses, and immunocompromised patients) relative to the general population; and (3) risk of serious illness in foods that support the growth of *L. monocytogenes* and in foods that do not support its growth at specific storage and shelf-life conditions (see p. 5 of Part 1 of the 2004 FAO/WHO *Listeria* risk assessment). The Executive Summary of the 2004 FAO/WHO *Listeria* risk assessment reports that the risk assessment found: (1) a considerable majority of cases are caused by foods with a level of contamination greater than 100 cfu/g at the time of consumption; (2) vulnerable populations have a greater risk of becoming ill compared to the general population, with the risk varying by group and underlying medical condition; and (3) RTE foods that support growth of *L. monocytogenes* increase the risk 100 to 1,000-fold compared to foods that do not support its growth (FAO/WHO 2004).

The 2004 FAO/WHO *Listeria* risk assessment was adopted by the Codex Alimentarius Commission (Codex 2007). (The Codex Alimentarius Commission was formed in 1963 by the FAO and WHO to develop food standards, guidelines, and related texts such as codes of practice, and is recognized under the World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures as the international standards organization for food safety). Codex's current recommendation for *L. monocytogenes* in RTE foods that do not support its growth aligns with the conclusions of the 2004 FAO/WHO *Listeria* risk assessment and supports a level of 100 cfu/g (FAO/WHO 2004) for specific products being manufactured in compliance with the fundamentals of food hygiene. These fundamentals include: the design of equipment and facilities to separate raw and finished product; the proper cleaning and disinfection of the food processing facility to prevent harborage of *L. monocytogenes*; a proper ventilation system to prevent condensation and aerosolization of *L. monocytogenes*; the use of validated listeriacidal treatments when appropriate; the strict temperature control of foods; the prevention of cross-contamination; and environmental monitoring to verify *L. monocytogenes* control. Additionally, the guidelines provide a sampling plan in support of the 100 cfu/g standard, as well as the flexibility for different criteria to be applied when the competent authority determines that an alternative approach provides an appropriate level of protection for public health.

Both the 2003 FDA/FSIS *Listeria* risk assessment and the 2004 FAO/WHO *Listeria* risk assessment are quantitative risk assessments that used mathematical modeling to estimate risk and assumed that individuals in a population may have varying susceptibility to infection. The dose-response models developed in these risk assessments are non-threshold models that assume that a single cell has the potential to infect and provoke a response in an individual (Codex 2007). As a result, under these models, the risk presented by foodborne *L. monocytogenes* does not reach zero unless the number of *L. monocytogenes* cells in a serving of food is zero. Another consequence of the non-threshold model is that an increase in either the frequency of contamination (percentage of food servings that are contaminated) or the level of contamination (cfu/g in a contaminated food serving) is expected to result in an increase in risk of listeriosis

(see p. 138 of Part 5; FAO/WHO 2004). Conversely, a decrease in either the frequency of contamination or the level of contamination is expected to result in a decrease in the risk of listeriosis.

Key differences between the 2003 FDA/FSIS *Listeria* risk assessment and the 2004 FAO/WHO *Listeria* risk assessment include: aspects of their focus (i.e., the questions that they addressed); modeling assumptions; sources of data regarding exposure; estimation of serving size; and reported output (FDA/HHS 2008a). See Table 1 in section VIII.A of this document for a comparison of some of these differences.

VI. 2008 Draft Compliance Policy Guide and Notice of Public Meeting

In a notice published in the *Federal Register* on February 7, 2008 (FDA/HHS 2008b), FDA issued for public comment a draft Compliance Policy Guide (the 2008 draft CPG) (FDA/HHS 2008a) that, if finalized, would establish an enforcement policy for *L. monocytogenes* in RTE foods based on whether the food does or does not support its growth as follows:

- For RTE foods that support the growth of *L. monocytogenes*, the 2008 draft CPG states that FDA may regard the food as adulterated within the meaning of section 402(a)(1) of the FD&C Act when *L. monocytogenes* is present in the food, based on an analytical method that can confirm the presence of *L. monocytogenes* per 25 gram (g) samples of food (i.e., less than 1.0 cfu/25 g or 0.04 cfu/g).
- For RTE foods that do not support the growth of *L. monocytogenes*, the 2008 draft CPG states that FDA may regard the food as adulterated within the meaning of section 402(a)(1) of the FD&C Act when *L. monocytogenes* is present at or above 100 cfu/g of food.

In a separate notice published in the *Federal Register* on February 7, 2008 (FDA/HHS 2008a), FDA announced a public meeting to discuss the 2008 draft CPG. In that notice, FDA explained how it took the output data of the model used in the 2003 FDA/FSIS *Listeria* risk assessment and re-tabulated the data to show its estimates of the annual number of cases of listeriosis in the elderly population, the intermediate-age population, and the neonatal population, as well as in the total population, as a function of the ingested dose (i.e., number of *L. monocytogenes* cells consumed) ("the 2008 FDA re-tabulation").

The 2008 FDA re-tabulation estimated that there would be no annual cases of listeriosis in the total population if all servings of RTE foods were at or below 10^5 cfu/serving (corresponding to 10^3 cfu/g or less for a 100 g serving of food) (FDA/HHS 2008a). Additionally, the 2008 FDA re-tabulation estimated that the median number of cases of listeriosis would be approximately 1 per year in the total population from all the servings that are contaminated with 10^7 cfu/serving or less (corresponding to 10^5 cfu/g or less for a 100 g serving of food) and approximately 6 per

year in the total population from all the servings that are contaminated with up to and including 10^8 cfu/serving (corresponding to 10^6 cfu/g for a 100 g serving of food) (FDA/HHS 2008a).

The findings of the 2003 FDA/FSIS *Listeria* risk assessment and the 2008 FDA re-tabulation support a conclusion that differences in risk of listeriosis are linked to the ability of an RTE food to support the growth of *L. monocytogenes* (FDA/HHS 2008a). Therefore, in the 2008 draft CPG, FDA regarded RTE foods differently based on whether the food does or does not support the growth of *L. monocytogenes*.

FDA received several comments on the 2008 draft CPG, including comments from industry, trade organizations, consumer advocacy groups, and another Federal agency (i.e., FSIS). Although some comments support both criteria in the 2008 draft CPG (i.e., the criterion for RTE foods that support the of growth of *L. monocytogenes* and the criterion for RTE foods that do not support growth of *L. monocytogenes*), other comments express concern about whether or not the criterion for RTE foods that do not support the growth of *L. monocytogenes* is adequate to protect public health.

VII. 2008 Draft Guidance for Industry on Control of *Listeria monocytogenes* in Refrigerated or Frozen Ready-To-Eat Foods

Any time a food is exposed to the environment during a manufacturing, processing, packing, or holding activity, there is the potential for the food to be contaminated with pathogenic microorganisms. *L. monocytogenes* is considered to be an "environmental pathogen" because it is capable of surviving and persisting within the manufacturing, processing, packing, or holding environment such that food may be contaminated and this contamination may result in foodborne illness if the food is consumed without treatment to significantly minimize *L. monocytogenes* after the food has been contaminated.

Appropriate sanitation controls can minimize the presence of environmental pathogens such as *L. monocytogenes* in the plant and the transfer of environmental pathogens to food-contact surfaces and to food (ICMSF 2002). Monitoring the food production environment for the presence of *L. monocytogenes* or the indicator organism *Listeria* spp. in facilities where food is manufactured, processed, packed or held can verify the effectiveness of sanitation controls. To do so, environmental monitoring must be designed to find sources of *L. monocytogenes* that remain in the facility in spite of routine cleaning and sanitizing (particularly strains that may have become established in the facility as resident strains, i.e., become established in a harborage site) so that the *L. monocytogenes* in those sites can be eliminated by appropriate corrective actions (e.g., intensified cleaning and sanitizing, sometimes involving equipment disassembly, and repairs to equipment or the facility to improve sanitary design). A robust environmental monitoring program for *L. monocytogenes* can detect the pathogen and enable the facility to eliminate it from the food production environment (including from harborage sites), thereby preventing

contamination of food with these pathogens and consequently, preventing foodborne illnesses (Codex 2007; Scott et al. 2005; Tompkin 2002; Tompkin et al. 1999).

In 2008, FDA issued a draft guidance for industry (the 2008 draft GFI) (FDA/HHS 2008c) entitled "Guidance for Industry: Control of *Listeria monocytogenes* in Refrigerated or Frozen Ready-To-Eat Foods; Draft Guidance). The 2008 draft GFI was, in part intended to encourage industry to focus resources on controlling *L. monocytogenes* in the production environment for the foods that presented the greatest risk of foodborne listeriosis (i.e., foods that support growth of *L. monocytogenes*), while maintaining appropriate sanitation programs for the production environment of foods that do not support growth. The 2008 draft GFI included recommendations for sanitation and environmental monitoring.

In the 2008 draft GFI, we recommended that a food processor who detects contamination of a critical food-contact surface or food with the indicator organism *Listeria* spp. either conduct a test to determine whether the *Listeria* spp. is *L. monocytogenes*, or assume that the *Listeria* spp. is *L. monocytogenes*. This recommendation differs in some respects from guidance issued by FSIS regarding the control of *Listeria* in RTE meat and poultry establishments. FSIS has established regulations requiring official establishments that produce RTE meat or poultry products exposed to the processing environment after the basic lethality procedure (e.g., cooking) to prevent product adulteration by *L. monocytogenes*. FSIS requires an establishment that produces post-lethality exposed RTE product to meet the specific requirements of one of three alternative programs for addressing *L. monocytogenes* (9 CFR 430.4(b)). FSIS has issued guidelines (the FSIS *Listeria* Compliance Guideline) to help establishments that produce RTE meat or poultry products exposed to the processing environment after the basic lethality procedure to comply with these requirements (FSIS 2014). Under the FSIS *Listeria* Compliance Guideline, an FSIS-regulated establishment that produces lower risk products (e.g., those treated with antimicrobial agents or other treatments to control *L. monocytogenes*) must take corrective actions (i.e., intensify the cleaning and sanitizing of the affected food-contact surface) if it receives a positive test result for an indicator organism on a food-contact surface. As part of these corrective actions the establishment should retest the affected food-contact surface and take additional corrective actions (intensified each time the test is positive for the indicator organism). The establishment should conduct additional testing until the affected food-contact surface is negative for the indicator organism. The FSIS *Listeria* Compliance Guideline does not recommend that these lower risk establishments determine whether *Listeria* species is *L. monocytogenes*, or assume that the *Listeria* species is *L. monocytogenes*, after a routine environmental sample initially tests positive for *Listeria* species. However, higher risk establishments (e.g., those that produce deli meat or hotdogs using sanitation alone to control *L. monocytogenes*) are required to hold the product after a second positive result on a food contact surface and test it for *L. monocytogenes* using a statistically based sampling methodology (9 CFR 430.4(b)3(ii)(B) and (C)).

VIII. Post-2008 Scientific Developments

Since issuing the 2008 draft CPG, FDA and FSIS, in consultation with CDC, conducted a quantitative, scientific assessment of (1) the risk of listeriosis posed by consumption of RTE foods commonly prepared and sold in delicatessens in retail food stores and (2) how that risk may be impacted by changes in practice. In addition, we have gathered data from an updated risk assessment model, increased disease surveillance, comprehensive epidemiology studies, and the Reportable Food Registry. As discussed immediately below, these new data have provided additional information on the relative risk and incidence of listeriosis among various subpopulations; the food products most often found to be contaminated with *L. monocytogenes*; and the food products most often associated with foodborne listeriosis.

A. 2013 FDA/FSIS Listeria *Risk Assessment of RTE Foods Prepared and Sold in Delicatessens and Retail Stores*

In 2013, FDA and FSIS, in consultation with CDC, published a quantitative, scientific assessment (the 2013 FDA/FSIS *Listeria* risk assessment) of (1) the risk of listeriosis posed by consumption of RTE foods commonly prepared and sold in delicatessens in retail food stores and (2) how that risk may be impacted by changes in practices in the deli (FDA-FSIS 2013). An interagency workgroup developed a retail-to-table model, including dynamic cross-contamination modeling, designed to evaluate RTE deli meats, cheeses, and salads that are (1) sliced, prepared, and/or packaged in the retail deli environment and consumed at home; and (2) sold in a range of retail settings. The 2013 FDA/FSIS *Listeria* risk assessment evaluated "what if" scenarios, relative to specified baseline conditions, to estimate the change in listeriosis risk that would occur with various changes in practices in the deli. Key findings of the 2013 FDA/FSIS *Listeria* risk assessment include: (1) Employing practices that prevent bacterial growth dramatically reduced the predicted risk of listeriosis; (2) cross contamination of *L. monocytogenes* in the retail environment dramatically increased the predicted risk of listeriosis; (3) increasing the concentration and transfer of *L. monocytogenes* from incoming products, the environment, or niches directly increased the predicted risk of illness; (4) sanitation practices that eliminate *L. monocytogenes* from deli food-contact surfaces resulted in a reduction in the predicted risk of illness; and (5) the slicer is a primary source of *L. monocytogenes* cross contamination for deli meats and cheeses.

B. 2015 FDA Listeria *Dose-Response Model*

Dose-response models, which quantify the relationship between an exposure dose and the probability of adverse health outcomes, were essential components of the risk assessments discussed in this document. However, because of data gaps and limitations in the available data and modeling approaches, considerable uncertainty existed. In 2011, the Interagency Risk Assessment Consortium (IRAC) and the Joint Institute for Food Safety and Applied Nutrition (JIFSAN) co-organized a workshop to: (1) Discuss the need to incorporate new data and *L.*

monocytogenes dose-response models in future risk assessments; (2) identify novel strategies for *L. monocytogenes* dose-response modeling, particularly the development of mechanistic microbial dose-response models; and (3) identify key factors and data to be considered in future dose-response modeling (Hoelzer et al. 2011).

Following the 2011 workshop, the Center for Food Safety and Applied Nutrition (CFSAN) published a reassessment of dose-response data from the 2003 FDA/FSIS *Listeria* risk assessment (Pouillot 2015). In that publication, CFSAN describes a model (the 2015 FDA *Listeria* dose-response model) that adjusts for variation in *L. monocytogenes* strain virulence and host susceptibility over 11 population subgroups with various comorbidities. Overall, the results obtained from the 2015 FDA *Listeria* dose-response model suggest that most listeriosis cases are linked to the ingestion of food contaminated with medium to high concentrations (doses between 3.5 and 7.5 log cfu/serving (between 3,100 and 31,000,000 cells)) of *L. monocytogenes* (Pouillot 2015). However, the 2015 FDA *Listeria* dose-response model also suggests that those population subgroups at greatest risk of developing listeriosis are also at a measurable risk of illness when consuming food contaminated with lower doses of *L. monocytogenes*. Specifically, CFSAN estimated that doses of 4 log cfu/ serving (10,000 cells per 100 gram serving, or 100 cfu/g) or lower are responsible for 2% of cases among healthy adults, but 4% of cases among pregnant women and 5% of cases among individuals with hematologic cancer, especially when a highly virulent *L. monocytogenes* strain is involved. The results obtained from the 2015 FDA *Listeria* dose-response model raise questions about whether a 100 cfu/g limit (assuming 100 g serving size) provides an appropriate level of protection for the most vulnerable populations when food is contaminated by highly virulent strains.

Differences between the 2003 FDA/FSIS *Listeria* risk assessment, the 2004 FAO/WHO *Listeria* risk assessment, the 2008 FDA re-tabulation, and the 2015 FDA *Listeria* dose-response model do not make the results of the 2015 FDA *Listeria* dose-response model directly comparable to the output presented in the earlier analyses. Examples of these differences include the maximum concentration to which *L. monocytogenes* can grow, the serving size, and the treatment of strain virulence and individual susceptibility. However, in general, the results of the 2015 FDA *Listeria* dose-response model estimate that there would be more annual cases of listeriosis at lower dose levels than had been estimated in either the 2008 FDA re-tabulation or the 2004 FAO/WHO *Listeria* risk assessment.

Table 1 describes some of the differences between the 2003 FDA/FSIS *Listeria* risk assessment, the 2004 FAO/WHO *Listeria* risk assessment, the 2008 FDA re-tabulation, and the 2015 FDA *Listeria* dose-response model. Table 1 also compares information about the estimated cases per dose as reported by each of these documents. For example:

- Table 2.19 in the 2004 FAO/WHO *Listeria* risk assessment estimates that there would be 12 of 2090 annual cases (0.574% of cases) in the susceptible population when the ingested dose is $10^{4.5}$ cfu/serving.

- The 2008 FDA re-tabulation estimates that there would be no annual cases of listeriosis in the total population if all servings of RTE foods were below 10^5 cfu/serving (FDA/HHS 2008a).

- The 2015 FDA *Listeria* dose-response model estimates that 230 of 1591 cases (14.5%) will occur at or below 10^5 cfu/serving) (Pouillot 2015).

Table 1. Comparison of the 2003 FDA/FSIS *Listeria* risk assessment, the 2004 FAO/WHO *Listeria* risk assessment, the 2008 FDA re-tabulation, and the 2015 FDA *Listeria* dose-response model

	2003 FDA/FSIS *Listeria* Risk Assessment	2004 FAO/WHO *Listeria* Risk Assessment	2008 FDA Re-Tabulation of Output of the 2003 FDA/FSIS *Listeria* Risk Assessment	2015 FDA *Listeria* Dose-Response Model
Type of dose-response model	Non-threshold* (mixture of models, mostly exponential model)	Non-threshold (exponential model)	Non-threshold (mixture of models, mostly exponential model)	Non-threshold (lognormal Poisson model)
Focus (questions that the risk assessment or model addressed)	Rank the risk of listeriosis for 23 categories of RTE food in the US to better target management strategies	Various. This table focusses on the answer to CCFH question number 1: Estimate the risk of listeriosis from *L. monocytogenes* in food when the number of organisms ranges from absence in 25 grams to 1,000 cfu/g, or does not exceed specified levels at the point of consumption.	Application of the FDA/FSIS 2003 model to estimate the annual number of cases of listeriosis in the total US population, and three subpopulations, as a function of the ingested dose (cfu/serving)	Answer short term recommendations from a workshop on *Listeria* dose-response, and incorporate adjustments into the *Listeria* dose-response model to specifically and separately characterize variability in strain virulence and host susceptibility

	2003 FDA/FSIS *Listeria* Risk Assessment	2004 FAO/WHO *Listeria* Risk Assessment	2008 FDA Re-Tabulation of Output of the 2003 FDA/FSIS *Listeria* Risk Assessment	2015 FDA *Listeria* Dose-Response Model
Key dose- response modeling assumptions	• Three population groups (perinatal, elderly, intermediate age) • Integrated distribution of strain virulence and individual susceptibility within sub population; • The maximum concentration to which *L. monocytogenes* could grow in a food is 10^8 cfu/g** (assuming growth between retail and consumption)	• Two population groups (with increased vs. decreased susceptibility) • No specific consideration of variability in strain virulence (averaged in the dose-response); • The maximum concentration to which *L. monocytogenes* could grow in a food is 10^7 to 10^{10} cfu/g (assuming growth between retail and consumption)	Same as for the 2003 FDA/FSIS *Listeria* risk assessment	• Distribution of strain virulence (based on 2003 FDA/FSIS *Listeria* risk assessment; • Distribution of individual susceptibility (based on 2003 FDA/FSIS *Listeria* risk assessment); • The maximum concentration to which *L. monocytogenes* could grow in a food is $10^{6.1}$ cfu/g (conservative assumptions: assuming no growth between retail and consumption; assuming contamination from 8 RTE categories is contamination from all RTE foods)
Serving size	Variable; empirical distributions derived from consumption surveys	Uniform serving size of 31.6 grams	Uniform serving size of 100 grams	Uniform serving size of 50 grams
Output most relevant to the comparison in this document	• Predicted risk of listeriosis for each of the 23 categories of RTE foods on both a per serving basis (risk to individual) and per annum basis (risk to U.S. population). • Estimates for total U.S. population and 3 age-based subpopulations.	Tables that report the annual incidence of listeriosis estimated to be associated with specific ingested doses of *L. monocytogenes****	Estimates of the annual number of cases of listeriosis in the elderly population, the intermediate-age population, the neonatal population, and the total population, as a function of the ingested dose	Probability of illness and expected number of cases in selected population subgroups and in the whole population as a function of the dose, considering individual susceptibility within groups, strain variability, and dose variability for a given mean dose

	2003 FDA/FSIS *Listeria* Risk Assessment	2004 FAO/WHO *Listeria* Risk Assessment	2008 FDA Re-Tabulation of Output of the 2003 FDA/FSIS *Listeria* Risk Assessment	2015 FDA *Listeria* Dose-Response Model
Expected dose at which there are no annual cases of listeriosis (if all food at this level)	There is a probability of illness for all doses above zero exposure.	• There is a probability of illness for all doses above zero exposure. • <1 annual case in the susceptible population expected at or below $10^{1.5}$ cfu/serving	• There is a probability of illness for all doses above zero exposure. • <0.1 annual case expected at or below 10^{5} cfu/serving	• There is a probability of illness for all doses above zero exposure. • 1 case expected at or below 10^{1} cfu/serving
Estimated annual cases of listeriosis at the low end of the dose response curve (with the food contamination distribution estimated in the study)	The number of cases is estimated separately for each of the 23 categories of foods.	• 1 annual case in the susceptible population at up to $10^{2.5}$ cfu/serving • 2 annual cases at up to $10^{3.5}$ cfu/serving • 12 annual cases at up to $10^{4.5}$ cfu/serving	• No annual cases at up to 10^{5} cfu/serving • 1 annual case at up to 10^{7} cfu/serving • 6 annual cases at up to 10^{8} cfu/serving	• 1 annual case at up to 10^{1} cfu/serving • 2 annual cases at up to $10^{1.5}$ cfu/serving • 55 annual cases at up to 10^{4} cfu/serving • 230 annual cases at up to 10^{5} cfu/serving

* The non-threshold model assumes that a single cell has the potential to infect and provoke a response in an individual. As a result: (1) the risk of listeriosis does not reach zero unless the number of *L. monocytogenes* in a food serving is zero; and (2) an increase in the dose will result in an increase in the predicted probability of listeriosis.

** A more virulent strain would have the potential to cause listeriosis with fewer cells than a less virulent strain.

*** Table 2.19 in Part 2 of the 2004 FAO/WHO *Listeria* Risk Assessment shows the impact of several assumptions about the maximum dose to which *L. monocytogenes* could grow in a food on their estimate of the annual number of illnesses in the susceptible population. For the purpose of this document, FDA is focusing on the most conservative assumption shown in Table 2.19 of the 2004 FAO/WHO *Listeria* Risk Assessment – i.e., the maximum dose to which *L. monocytogenes* could grow in a food is $10^{7.5}$ cfu/serving.

C. Disease Surveillance and Epidemiological Studies

A landmark study covering 1,959 cases of listeriosis reported between 2001 and 2009 in France assesses the relative risk of listeriosis for persons less than 65 years of age with no underlying medical condition compared to that of distinct sub-populations (such as the elderly, pregnant women and their fetuses, and persons with certain medical conditions) (Goulet 2012). Those with chronic lymphocytic leukemia had a greater than 1000-fold increased risk of developing listeriosis compared to a healthy adult aged less than 65 years, while adults aged 65 – 74 years with no underlying condition had an 8-fold increase in risk of contracting listeriosis. The study recommends that strict dietary recommendations should be aimed at individuals with a high risk of infection (Goulet 2012). Likewise, in 2012, Pouillot et al. found that incidence rates from FoodNet (Foodborne Diseases Active Surveillance Network) data demonstrate a gradual, increased risk of listeriosis with age (Pouillot 2012).

A recent outbreak of listeriosis associated with consumption of contaminated ice cream may support the findings of the 2015 FDA *Listeria* dose-response model that some highly susceptible individuals are at risk for illness at lower levels of *L. monocytogenes*. Evidence obtained by FDA during the outbreak investigation suggests that about 99% of one ice cream product sold to institutions (e.g., hospitals, schools, and nursing homes) during the final months of 2014 was contaminated with low levels of *L. monocytogenes* (92% of samples in the 10-20 CFU/g range). Although the number of individuals who became ill was relatively small in light of the amount of product distributed, many of the affected individuals were in the vulnerable subpopulations and 3 individuals died.

Table 2 summarizes the key outbreaks of foodborne listeriosis in the United States since 2010. A relatively high percentage of these outbreaks (more than 75% of cases, and approximately 80% of deaths) have been associated with fresh produce or minimally processed produce (e.g., caramel apples). The outbreaks of foodborne listeriosis associated with consumption of fresh or minimally processed produce have led us to investigations of produce packinghouses, where insanitary conditions were found that may have led to the contamination of the produce (FDA/HHS 2011, 2012a, 2012b, 2014, 2015b).

Table 2. Key Outbreaks of Foodborne Listeriosis in the United States since 2010

Year	Implicated Food	Number of Cases	Number of Deaths	Reference
2010-2015	Ice cream	10	3	CDC 2015a
2014	Caramel Apples	35	7	CDC 2015b
2014	Sprouts	5	2	CDC 2015c
2013 - 2014	Cheese and dairy products	5	1	CDC 2014b
2013	Cheese products	8	1	CDC 2014c
2013	Cheeses	6	1	CDC 2013
2012	Ricotta salata cheese	22	4	CDC 2012a
2011	Cantaloupe	147	33	CDC 2011

D. Reports to the Reportable Food Registry

In September 2009, FDA established an electronic portal - the Reportable Food Registry (RFR) - to which reports about instances of reportable food must be submitted to FDA within 24 hours by responsible parties. (A reportable food is an article of human or animal food for which there is a reasonable probability that the use of, or exposure to, such article of food will cause serious

adverse health consequences or death to humans or animals). Table 3 shows the distribution of RFR entries for *L. monocytogenes* by commodity for the first 4 years of the RFR.

Table 3. Reports to the Reportable Food Registry for *Listeria monocytogenes*

Commodity	Year 1 No.	Year 1 Percent	Year 2 No.	Year 2 Percent	Year 3 No.	Year 3 Percent	Year 4 No.	Year 4 Percent
Bakery	0	0.0%	0	0.0%	0	0.0%	1	2.9%
Dairy	8	24.2%	7	17.5%	11	22.9%	4	11.4%
Dressing/Sauces/ Gravies	1	3.0%	0	0.0%	0	0.0%	0	0.0%
Egg	0	0.0%	2	5.0%	2	4.2%	0	0.0%
Frozen Foods	3	9.0%	1	2.5%	1	2.1%	0	0.0%
Fruit and Vegetable Products	2	6.0%	2	5.0%	0	0.0%	1	2.9%
Meal Replacement/ Nutritional Food and Beverages	1	3.0%	0	0.0%	0	0.0%	0	0.0%
Multiple Products	1	3.0%	0	0.0%	0	0.0%	0	0.0%
Nuts/Nut Products/Seed Products	1	3.0%	0	0.0%	0	0.0%	2	5.7%
Prepared Foods	2	6.0%	10	25.0%	5	10.4%	4	11.4%
Produce - Fresh Cut	5	15.1%	7	17.5%	15	31.3%	7	20.0%
Produce - Raw Agricultural Commodity	0	0.0%	2	5.0%	10	20.8%	3	8.6%
Seafood	9	27.2%	8	20.0%	4	8.3%	12	34.3%
Stabilizers/Emulsifiers/Flavors/Colors/	0	0.0%	1	2.5%	0	0.0%	1	2.9%
Total	33	100%	40	100%	48	100%	35	100%

The foods most commonly involved in reports to the RFR for the presence of *L. monocytogenes* are seafood, dairy products, prepared foods such as RTE salads and sandwiches, and fresh cut produce.

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